03-26-01

JC14 Rec'd PCT/PTO 22 MAR 2001

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FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER	
12964.23	
U S APPLICATION NO (If known, see 37 CFR 1 5)	
09/806080	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/07055	22 September 1999	22 September 1998

TITLE OF INVENTION: GENES OF THE 1-DEOXY D-XYLULOSE BIOSYNTHESIS PATHWAY

APPLICANT(S) FOR DO/EO/US: JOMAA, Hassan

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [X] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [X] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). unsigned
10. [X] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [X] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information: Express Mail Certificate
    Post card

JC10 Rec'd PCT/PTO 22 MAR 2001

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/806080	PCT/EP99/07055	12964.23

21. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [X] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	40 - 20 =	20	x **$18.00**	$ 360.00	
Independent claims	8 - 3 =	5	x **$80.00**	$ 400.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$ 270.00	
TOTAL OF ABOVE CALCULATIONS =				$ 2020.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$ n/a	
SUBTOTAL =				$ 2020.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$ n/a	
TOTAL NATIONAL FEE =				$ 2020.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00	
TOTAL FEES ENCLOSED =				$ 2060.00	
				Amount to be refunded:	$
				charged:	$

a. [X] A check in the amount of $ 2060.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. 08-1394 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-1394 . A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Warren B. Kice

Haynes and Boone, LLP
901 Main Street, Suite 3100
Dallas, Texas 75202
Phone: 214-651-5634
Fax: 214-651-5940

SIGNATURE

Warren B. Kice

NAME

22,732

REGISTRATION NUMBER

RAW SEQUENCE LISTING DATE: 04/16/2001
PATENT APPLICATION: US/09/806,080 TIME: 10:33:02

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  7 <130> FILE REFERENCE: 15696
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C--> 10 <141> CURRENT FILING DATE: 2001-03-22
 12 <150> PRIOR APPLICATION NUMBER: DE19923567.8
 13 <151> PRIOR FILING DATE: 1999-05-22
 15 <150> PRIOR APPLICATION NUMBER: DE19843279.8
 16 <151> PRIOR FILING DATE: 1998-09-22
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 46              20                  25                  30
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 52 gat aat aaa ata aca aag agt aga aga tgt aaa aga ata aag tta tgc   192
 53 Asp Asn Lys Ile Thr Lys Ser Arg Arg Cys Lys Arg Ile Lys Leu Cys
 54      50                  55                  60
 56 aaa aag gat tta ata gat att ggt gca ata aag aaa cca att aat gta   240
 57 Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val
 58  65                  70                  75                  80
 60 gca att ttt gga agt act ggt agt ata ggt acg aat gct tta aat ata   288
 61 Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile
 62                  85                  90                  95
 64 ata agg gag tgt aat aaa att gaa aat gtt ttt aat gtt aaa gca ttg   336
 65 Ile Arg Glu Cys Asn Lys Ile Glu Asn Val Phe Asn Val Lys Ala Leu
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 68 tat gtg aat aag agt gtg aat gaa tta tat gaa caa gct aga gaa ttt   384
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PATENT APPLICATION: US/09/806,080 TIME: 10:33:02

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 74     130                 135                 140
 76 aaa gaa ctg gta aaa aat ata aaa gat tat aaa cct ata ata ttg tgt   480
 77 Lys Glu Leu Val Lys Asn Ile Lys Asp Tyr Lys Pro Ile Ile Leu Cys
 78 145                 150                 155                 160
 80 ggt gat gaa ggg atg aaa gaa ata tgt agt agt aat agt ata gat aaa   528
 81 Gly Asp Glu Gly Met Lys Glu Ile Cys Ser Ser Asn Ser Ile Asp Lys
 82                 165                 170                 175
 84 ata gtt att ggt att gat tct ttt caa gga tta tat tct act atg tat   576
 85 Ile Val Ile Gly Ile Asp Ser Phe Gln Gly Leu Tyr Ser Thr Met Tyr
 86             180                 185                 190
 88 gca att atg aat aat aaa ata gtt gcg tta gct aat aaa gaa tcc att   624
 89 Ala Ile Met Asn Asn Lys Ile Val Ala Leu Ala Asn Lys Glu Ser Ile
 90         195                 200                 205
 92 gtc tct gct ggt ttc ttt tta aag aaa tta tta aat att cat aaa aat   672
 93 Val Ser Ala Gly Phe Phe Leu Lys Lys Leu Leu Asn Ile His Lys Asn
 94     210                 215                 220
 96 gca aag ata ata cct gtt gat tca gaa cat agt gct ata ttt caa tgt   720
 97 Ala Lys Ile Ile Pro Val Asp Ser Glu His Ser Ala Ile Phe Gln Cys
 98 225                 230                 235                 240
100 tta gat aat aat aag gta tta aaa aca aaa tgt tta caa gac aat ttt   768
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102                 245                 250                 255
104 tct aaa att aac aat ata aat aaa ata ttt tta tgt tca tct gga ggt   816
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106             260                 265                 270
108 cca ttt caa aat tta act atg gac gaa tta aaa aat gta aca tca gaa   864
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112 aat gct tta aag cat cct aaa tgg aaa atg ggt aag aaa ata act ata   912
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118 305                 310                 315                 320
120 ttt tta ttt gat gta gat tat aat gat ata gaa gtt ata gta cat aaa  1008
121 Phe Leu Phe Asp Val Asp Tyr Asn Asp Ile Glu Val Ile Val His Lys
122                 325                 330                 335
124 gaa tgc att ata cat tct tgt gtt gaa ttt ata gac aaa tca gta ata  1056
125 Glu Cys Ile Ile His Ser Cys Val Glu Phe Ile Asp Lys Ser Val Ile
126             340                 345                 350
128 agt caa atg tat tat cca gat atg caa ata ccc ata tta tat tct tta  1104
129 Ser Gln Met Tyr Tyr Pro Asp Met Gln Ile Pro Ile Leu Tyr Ser Leu
130         355                 360                 365
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RAW SEQUENCE LISTING DATE: 04/16/2001
PATENT APPLICATION: US/09/806,080 TIME: 10:33:02

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138 385                 390                 395                 400
140 tgt att aaa tta gct tat caa gca ggt ata aaa gga aac ttt tat cca   1248
141 Cys Ile Lys Leu Ala Tyr Gln Ala Gly Ile Lys Gly Asn Phe Tyr Pro
142                 405                 410                 415
144 act gta cta aat gcg tca aat gaa ata gct aac aac tta ttt ttg aat   1296
145 Thr Val Leu Asn Ala Ser Asn Glu Ile Ala Asn Asn Leu Phe Leu Asn
146             420                 425                 430
148 aat aaa att aaa tat ttt gat att tcc tct ata ata tcg caa gtt ctt   1344
149 Asn Lys Ile Lys Tyr Phe Asp Ile Ser Ser Ile Ile Ser Gln Val Leu
150         435                 440                 445
152 gaa tct ttc aat tct caa aag gtt tcg gaa aat agt gaa gat tta atg   1392
153 Glu Ser Phe Asn Ser Gln Lys Val Ser Glu Asn Ser Glu Asp Leu Met
154     450                 455                 460
156 aag caa att cta caa ata cat tct tgg gcc aaa gat aaa gct acc gat   1440
157 Lys Gln Ile Leu Gln Ile His Ser Trp Ala Lys Asp Lys Ala Thr Asp
158 465                 470                 475                 480
160 ata tac aac aaa cat aat tct tca tag                              1467
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162                 485
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166 <211> LENGTH: 488
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168 <213> ORGANISM: Plasmodium falciparum
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175             20                  25                  30
177 Arg Lys Asn Asn Ala Tyr Ile Asn Tyr Gly Ile Gly Tyr Asn Gly Pro
178         35                  40                  45
180 Asp Asn Lys Ile Thr Lys Ser Arg Arg Cys Lys Arg Ile Lys Leu Cys
181     50                  55                  60
183 Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val
184 65                  70                  75                  80
186 Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile
187                 85                  90                  95
189 Ile Arg Glu Cys Asn Lys Ile Glu Asn Val Phe Asn Val Lys Ala Leu
190             100                 105                 110
192 Tyr Val Asn Lys Ser Val Asn Glu Leu Tyr Glu Gln Ala Arg Glu Phe
193         115                 120                 125
195 Leu Pro Glu Tyr Leu Cys Ile His Asp Lys Ser Val Tyr Glu Glu Leu
196     130                 135                 140
198 Lys Glu Leu Val Lys Asn Ile Lys Asp Tyr Lys Pro Ile Ile Leu Cys
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201 Gly Asp Glu Gly Met Lys Glu Ile Cys Ser Ser Asn Ser Ile Asp Lys
202                 165                 170                 175
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RAW SEQUENCE LISTING DATE: 04/16/2001
PATENT APPLICATION: US/09/806,080 TIME: 10:33:02

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207 Ala Ile Met Asn Asn Lys Ile Val Ala Leu Ala Asn Lys Glu Ser Ile
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210 Val Ser Ala Gly Phe Phe Leu Lys Lys Leu Leu Asn Ile His Lys Asn
211     210                 215                 220
213 Ala Lys Ile Ile Pro Val Asp Ser Glu His Ser Ala Ile Phe Gln Cys
214 225                 230                 235                 240
216 Leu Asp Asn Asn Lys Val Leu Lys Thr Lys Cys Leu Gln Asp Asn Phe
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220             260                 265                 270
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223         275                 280                 285
225 Asn Ala Leu Lys His Pro Lys Trp Lys Met Gly Lys Lys Ile Thr Ile
226     290                 295                 300
228 Asp Ser Ala Thr Met Met Asn Lys Gly Leu Glu Val Ile Glu Thr His
229 305                 310                 315                 320
231 Phe Leu Phe Asp Val Asp Tyr Asn Asp Ile Glu Val Ile Val His Lys
232                 325                 330                 335
234 Glu Cys Ile Ile His Ser Cys Val Glu Phe Ile Asp Lys Ser Val Ile
235             340                 345                 350
237 Ser Gln Met Tyr Tyr Pro Asp Met Gln Ile Pro Ile Leu Tyr Ser Leu
238         355                 360                 365
240 Thr Trp Pro Asp Arg Ile Lys Thr Asn Leu Lys Pro Leu Asp Leu Ala
241     370                 375                 380
243 Gln Val Ser Thr Leu Thr Phe His Lys Pro Ser Leu Glu His Phe Pro
244 385                 390                 395                 400
246 Cys Ile Lys Leu Ala Tyr Gln Ala Gly Ile Lys Gly Asn Phe Tyr Pro
247                 405                 410                 415
249 Thr Val Leu Asn Ala Ser Asn Glu Ile Ala Asn Asn Leu Phe Leu Asn
250             420                 425                 430
252 Asn Lys Ile Lys Tyr Phe Asp Ile Ser Ser Ile Ile Ser Gln Val Leu
253         435                 440                 445
255 Glu Ser Phe Asn Ser Gln Lys Val Ser Glu Asn Ser Glu Asp Leu Met
256     450                 455                 460
258 Lys Gln Ile Leu Gln Ile His Ser Trp Ala Lys Asp Lys Ala Thr Asp
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262                 485
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267 <211> LENGTH: 3872
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272 <221> NAME/KEY: CDS
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275 <220> FEATURE:
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288 tatca atg att ttt aat tat gtg ttt ttt aag aac ttt gta cca gtt gtt 170
289       Met Ile Phe Asn Tyr Val Phe Phe Lys Asn Phe Val Pro Val Val
290         1               5                  10                  15
292 cta tac att ctc ctt ata ata tat att aac tta aat ggc atg aat aat   218
293 Leu Tyr Ile Leu Leu Ile Ile Tyr Ile Asn Leu Asn Gly Met Asn Asn
294                 20                  25                  30
296 aaa aat caa ata aaa aca gaa aaa att tat ata aag aaa ttg aat agg   266
297 Lys Asn Gln Ile Lys Thr Glu Lys Ile Tyr Ile Lys Lys Leu Asn Arg
298             35                  40                  45
300 ttg tca agg aaa aat tcg tta tgt agt tct aaa aat aaa ata gca tgc   314
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302         50                  55                  60
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306     65                  70                  75
308 aat gtg aat gtt aaa aat gat gat att aat tcc tta cta aaa aat aat   410
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310  80                  85                  90                  95
312 tat agt aat aaa ttg tac atg gat aag agg aaa aat att aat aat gta   458
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314                 100                 105                 110
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326     145                 150                 155
328 gat aat aat agg aat aat aaa aag aat ttt aat tta tta ttt ata aat   650
329 Asp Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn
330 160                 165                 170                 175
332 tat ttt aat ttg aaa cga atg aaa aat tct ctt cta aat aaa gac aat   698
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338             195                 200                 205
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VERIFICATION SUMMARY DATE: 04/16/2001
PATENT APPLICATION: US/09/806,080 TIME: 10:33:04

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L:9 M:270 C: Current Application Number differs, Replaced Current Application Number
L:10 M:271 C: Current Filing Date differs, Replaced Current Filing Date

PCT

RAW SEQUENCE LISTING DATE: 04/04/2001
PATENT APPLICATION: US/09/806,080 TIME: 11:20:05

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3 <110> APPLICANT: Jomaa, Hassan
5 <120> TITLE OF INVENTION: Gene des 1-Desoxy-D-xylulose-Biosynthesewegs
7 <130> FILE REFERENCE: 15696
C--> 9 <140> CURRENT APPLICATION NUMBER: US/09/806,080
C--> 10 <141> CURRENT FILING DATE: 2001-03-22
12 <150> PRIOR APPLICATION NUMBER: DE19923567.8
13 <151> PRIOR FILING DATE: 1999-05-22
15 <150> PRIOR APPLICATION NUMBER: DE19843279.8
16 <151> PRIOR FILING DATE: 1998-09-22
18 <160> NUMBER OF SEQ ID NOS: 6
20 <170> SOFTWARE: PatentIn Ver. 2.1

Does Not Comply
Corrected Diskette Needed
See p. 4

ERRORED SEQUENCES

597 <210> SEQ ID NO: 4
598 <211> LENGTH: 1205
599 <212> TYPE: PRT
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        35                  40                  45
Ser Arg Lys Asn Ser Leu Cys Ser Ser Lys Asn Lys Ile Ala Cys Leu
    50                  55                  60
Phe Asp Ile Gly Asn Asp Asp Asn Arg Asn Thr Thr Tyr Gly Tyr Asn
65                  70                  75                  80
Val Asn Val Lys Asn Asp Asp Ile Asn Ser Leu Leu Lys Asn Asn Tyr
                85                  90                  95
Ser Asn Lys Leu Tyr Met Asp Lys Arg Lys Asn Ile Asn Asn Val Ile
            100                 105                 110
Ser Thr Asn Lys Ile Ser Gly Ser Ile Ser Asn Ile Cys Ser Arg Asn
        115                 120                 125
Gln Lys Glu Asn Glu Gln Lys Arg Asn Lys Gln Arg Cys Leu Thr Gln
    130                 135                 140
Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn Asp
145                 150                 155                 160
Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn Tyr
                165                 170                 175
Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn Phe
            180                 185                 190
Phe Tyr Cys Lys Glu Lys Lys Leu Ser Phe Leu His Lys Ala Tyr Lys
        195                 200                 205
```

RAW SEQUENCE LISTING DATE: 04/04/2001
PATENT APPLICATION: US/09/806,080 TIME: 11:20:06

Input Set : A:\S0109991.app
Output Set: N:\CRF3\04042001\I806080.raw

```
642 Lys Lys Asn Cys Thr Phe Gln Asn Tyr Ser Leu Lys Arg Lys Ser Asn
643     210                 215                 220
645 Arg Asp Ser His Lys Leu Phe Ser Gly Glu Phe Asp Asp Tyr Thr Asn
646 225                 230                 235                 240
648 Asn Asn Ala Leu Tyr Glu Ser Glu Lys Lys Glu Tyr Ile Thr Leu Asn
649                 245                 250                 255
651 Asn Asn Asn Lys Asn Asn Asn Asn Lys Asn Asn Asp Asn Lys Asn Asn
652             260                 265                 270
654 Asp Asn Asn Asp Tyr Asn Asn Asn Asn Ser Cys Asn Asn Leu Gly Glu
655         275                 280                 285
657 Arg Ser Asn His Tyr Asp Asn Tyr Gly Gly Asp Asn Asn Asn Pro Cys
658     290                 295                 300
660 Asn Asn Asn Asn Asp Lys Tyr Asp Ile Gly Lys Tyr Phe Lys Gln Ile
661 305                 310                 315                 320
663 Asn Thr Phe Ile Asn Ile Asp Glu Tyr Lys Thr Ile Tyr Gly Asp Glu
664                 325                 330                 335
666 Ile Tyr Lys Glu Ile Tyr Glu Leu Tyr Val Glu Arg Asn Ile Pro Glu
667             340                 345                 350
669 Tyr Tyr Glu Arg Lys Tyr Phe Ser Glu Asp Ile Lys Lys Ser Val Leu
670         355                 360                 365
672 Phe Asp Ile Asp Lys Tyr Asn Asp Val Glu Phe Glu Lys Ala Ile Lys
673     370                 375                 380
675 Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn Thr
676 385                 390                 395                 400
678 Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His Tyr
679                 405                 410                 415
681 Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys Leu
682             420                 425                 430
684 Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe Leu
685         435                 440                 445
687 Phe Phe Ile Val Asn Ile Thr Gly Gly His Phe Ser Ser Val Leu Ser
688     450                 455                 460
690 Ser Leu Glu Ile Gln Leu Leu Leu Leu Tyr Ile Phe Asn Gln Pro Tyr
691 465                 470                 475                 480
693 Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys Ile
694                 485                 490                 495
696 Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys Gly
697             500                 505                 510
699 Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe Gly
700         515                 520                 525
702 Ala Gly His Ser Ser Thr Ser Leu Ser Ala Ile Gln Gly Tyr Tyr Glu
703     530                 535                 540
705 Ala Glu Trp Gln Val Lys Asn Lys Glu Lys Tyr Gly Asn Gly Asp Ile
706 545                 550                 555                 560
708 Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe Gln
709                 565                 570                 575
711 Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn Asn
712             580                 585                 590
714 Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn Val
```

RAW SEQUENCE LISTING DATE: 04/04/2001
PATENT APPLICATION: US/09/806,080 TIME: 11:20:06

Input Set : A:\S0109991.app
Output Set: N:\CRF3\04042001\I806080.raw

```
715         595                 600                 605
717 Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile Ala
718     610                 615                 620
720 Ile Ile Gly Asp Gly Gly Leu Thr Gly Gly Met Ala Leu Glu Ala Leu
721 625                 630                 635                 640
723 Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn Asp
724                 645                 650                 655
726 Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly Asn
727             660                 665                 670
729 Arg Pro Ile Gly Ser Ile Ser Asp His Leu His Tyr Phe Val Ser Asn
730         675                 680                 685
732 Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys Glu
733     690                 695                 700
735 Asn Asn Ile Phe Glu Asn Leu Asn Tyr Asp Tyr Ile Gly Val Val Asn
736 705                 710                 715                 720
738 Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys Glu
739                 725                 730                 735
741 Asn Lys Leu Lys Arg Ala Thr Val Leu His Val Arg Thr Lys Lys Ser
742             740                 745                 750
744 Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser Ile
745         755                 760                 765
747 Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly Asn
748     770                 775                 780
750 Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser Ser
751 785                 790                 795                 800
753 Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn Ser
754                 805                 810                 815
756 Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr Asp
757             820                 825                 830
759 Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn Ile
760         835                 840                 845
762 Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys Ile
763     850                 855                 860
765 Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu Gln
766 865                 870                 875                 880
768 His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu Lys
769                 885                 890                 895
771 Ile Gln Leu Cys Ile Tyr Ser Thr Phe Leu Gln Arg Ala Tyr Asp Gln
772             900                 905                 910
774 Ile Ile His Asp Leu Asn Leu Gln Asn Ile Pro Leu Lys Val Ile Ile
775         915                 920                 925
777 Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly Ile
778     930                 935                 940
780 Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile Ser
781 945                 950                 955                 960
783 Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr Leu
784                 965                 970                 975
786 Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile Leu
787             980                 985                 990
```

RAW SEQUENCE LISTING DATE: 04/04/2001
PATENT APPLICATION: US/09/806,080 TIME: 11:20:06

Input Set : A:\S0109991.app
Output Set: N:\CRF3\04042001\I806080.raw

```
     789 Ser Asp Lys Tyr Met Lys Gly Tyr Leu Asn Ile His Met Lys Asn Glu
     790         995                1000                1005
     792 Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp Lys
     793     1010                1015                1020
     795 Tyr Ser Glu Glu Tyr Met Asp Asp Asp Asn Phe Ile Lys Ser Phe Ile
E--> 796 025                1030                1035                1040
     798 Gly Lys Ser Arg Ile Ile Lys Met Asp Asn Glu Asn Asn Asn Thr Asn
     799                 1045                1050                1055
     801 Glu His Tyr Ser Ser Arg Gly Asp Thr Gln Thr Lys Lys Lys Lys Val
     802             1060                1065                1070
     804 Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala Ile
     805         1075                1080                1085
     807 Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe Ser
     808     1090                1095                1100
     810 Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile Asp
E--> 811 105                1110                1115                1120
     813 His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu Asp
     814                 1125                1130                1135
     816 Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile Glu
     817             1140                1145                1150
     819 Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr Leu
     820         1155                1160                1165
     822 Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu Val
     823     1170                1175                1180
     825 Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr Leu
E--> 826 185                1190                1195                1200
     828 Lys Asn Asn Pro Thr
     829                 1205
```

Invalid amino acid numbers.
Move numbers circled one space
to the right as shown below.

Tyr
1025

Ile
1105

Val
1185

VERIFICATION SUMMARY DATE: 04/04/2001
PATENT APPLICATION: **US/09/806,080** TIME: 11:20:07

Input Set : **A:\S0109991.app**
Output Set: **N:\CRF3\04042001\I806080.raw**

L:1 M:259 W: Allowed number of lines exceeded, (1) GENERAL INFORMATION:
L:9 M:270 C: Current Application Number differs, Replaced Current Application Number
L:10 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:796 M:332 E: (32) Invalid/Missing Amino Acid Numbering, SEQ ID:4
M:332, Repeated in SeqNo=4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Jomaa	§	Attorney Docket No.: 12964.23
Serial No.: United States National Phase of PCT/EP99/07055	§	I. A. Filing Date: 22 SEP1999
Filed: Herewith	§	Priority Date: 22 SEP 1998
For: GENES OF THE 1-DEOXY D-XYLULOSE BIOSYNTHESIS PATHWAY	§	

Attention: DO/EO/US
Commissioner For Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Prior to the initial examination of the above-identified application, please amend the application as follows:

IN THE CLAIMS:

6. (Amended) Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, characterized in that a DNA sequence according to claim 4 is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.

7. (Amended) Transgenic systems, in particular plants and plant cells which contain one or more DNA sequences according to one of claims 1 to 3 as "foreign" or "additional" DNA, which sequences are expressed.

8. (Amended) Expression vector containing one or more DNA sequences according to one of claims 1 to 3.

11. (Amended) Protein according to claim 9, characterized in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which hybridize with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would hybridize without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.

12. (Amended) Protein according to one of claims 1-3, 6, 9, 10, 11, 22 and 23 characterized in that it comprises the amino acid sequences SEQ ID no. 2, 4 or 6.

18. (Amended) Use of DNA according to one of claims 1 to 3.

Please add the following Claims 19-23.

19. Use of proteins according to claim 9.

20. Use of proteins according to Claim 10.

21. Use of transgenic systems according to claim 7 for the prevention or treatment of diseases in humans and animals.

22. Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, characterized in that a DNA sequence according to claim 5 is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.

23. Protein according to claim 10, characterized in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which hybridize with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would hybridize without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.

REMARKS

Claims 1-23 remain in the application. Claims 6, 7, 8, 11, 12 and 18 have been amended. Claims 19-23 have been added. The filing fee has been calculated according to the above-amendments.

Should the Examiner have any questions or comments regarding the amendments, the Examiner is invited to telephone the undersigned at the number listed below.

Respectfully submitted,

Warren B. Kice
Registration No. 22,732

Dated: 3/22/01

HAYNES AND BOONE, L.L.P.
901 Main Street, Suite 3100
Dallas, Texas 75202-3789
Telephone: 214/651-5634
Fax: 214/651-5940
Docket Number: 12964.23
D-880233.1

EXPRESS MAIL NO.: EL418590374US
DATE OF DEPOSIT: March 22, 2001

This paper and fee are being deposited with the U.S. Postal Service Express Mail Post Office to Addressee service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, Washington, D.C. 20231

SANDRA KUBIN
Name of person mailing paper and fee

Signature of person mailing paper and fee

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Jomaa	§	Attorney Docket No.: 12964.23
Serial No.: United States National Phase of PCT/EP99/07055	§	I. A. Filing Date: 22 SEP1999
Filed: Herewith	§	Priority Date: 22 SEP 1998
For: GENES OF THE 1-DEOXY D-XYLULOSE BIOSYNTHESIS PATHWAY	§	

Attention: DO/EO/US
Commissioner For Patents
Washington, D.C. 20231

REDLINE VERSION FOR PRELIMINARY AMENDMENT

6. (Amended) Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, [characterised] characterized in that a DNA sequence according to claim 4 [or 5] is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.

7. (Amended) Transgenic systems, in particular plants and plant cells which contain one or more DNA sequences according to one of claims 1 to [5]3 as "foreign" or "additional" DNA, which sequences are expressed.

8. (Amended) Expression vector containing one or more DNA sequences according to one of claims 1 to [5] 3.

11. (Amended) Protein according to [one of] claim[s] 9 [and 10], [characterised] characterized in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which [hybridise] hybridize with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would [hybridise] hybridize without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.

12. (Amended) Protein according to one of [the preceding] claims 1-3, 6, 9, 10, 11, 22 and 23 [characterised] characterized in that it comprises the amino acid sequences SEQ ID no. 2, 4 or 6.

18. (Amended) Use of DNA according to one of claims 1 to [5] 3. [or of proteins according to one of claims 9 to 12 or of transgenic systems according to claim 7 for the prevention or treatment of diseases in humans and animals.]

PATENT/DOCKET 12964.23

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Hassan Jomaa §

Serial No.: 09/806,080 § I. A. Filing Date: 22 SEP1999

Filed: March 22, 2001 § Priority Date: 22 SEP 1998

For: GENES OF THE 1-DEOXY D-XYLULOSE BIOSYNTHESIS PATHWAY

Attention: DO/EO/US
Box PCT
Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO COMPLY WITH REQUIREMENTS FOR SEQUENCE DISCLOSURES

Sir:

The information recorded in computer readable form (diskette sent with original filing on 22 March 2001) is identical to the written sequence listing.

We believe this response to complete the requirements under 35 U.S.C. 371.

Respectfully submitted,

Warren B. Kice
Reg. No. 22,732

Dated: 5/29/01

HAYNES AND BOONE, L.P.
901 Main Street, Suite 3100
Dallas, Texas 75202-3789
Telephone: 214/651-5634
Fax: 214/651-5940
Docket Number: 12964.23

D-900261.1

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner For Patents, Box PCT, Washington, D.C. 20231

on May 29, 2001

Sandra Kubin

SANDRA KUBIN

09/806080
PCT/EP99/07055
JC10 Rec'd PCT/PTO 22 MAR 2001

Genes of the 1-deoxy-D-xylulose biosynthesis pathway

The present invention relates to DNA sequences which, when incorporated into the genome of viruses, eukaryotes and prokaryotes, modify isoprenoid biosynthesis and to a genetic engineering process for the production of these transgenic viruses, eukaryotes and prokaryotes. The invention also relates to a process for the identification of substances having herbicidal, antimicrobial, antiparasitic, antiviral, fungicidal, bactericidal action in plants and antimicrobial, antiparasitic, antimycotic, antibacterial and antiviral action in humans and animals.

The biosynthesis pathway for the formation of isoprenoids via the classical acetate/mevalonate pathway and an alternative mevalonate-independent biosynthesis pathway, the deoxy-D-xylulose phosphate pathway is already known (Rohmer, M., Knani, M., Simonin, P., Sutter, B. and Sahm, H. (1993): *Biochem. J.* 295: 517-524).

It is, however, not known how and by which pathways it is possible to bring about a change in the isoprenoid concentration in viruses, eukaryotes and prokaryotes by means of the deoxy-D-xylulose phosphate pathway. Figure 1 shows this biosynthesis pathway.

DNA sequences are consequently provided which code for 1-deoxy-D-xylulase 5-phosphate synthase (DOXP synthase), 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DOXP reductoisomerase) or the gcpE protein. All three genes and enzymes are involved in isoprenoid biosynthesis.

(Translator's comment: The portion at the beginning of the next paragraph enclosed in square brackets corresponds to the beginning of the sentence which finishes on page 2, line 1 of the original).

[The gcpE protein has a kinase function and catalyses the phosphorylation of a sugar or a phosphorus sugar or a precursor of isoprenoid biosynthesis, in particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erytritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose] phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate. In the precursor of isoprenoid synthesis, the gcpE protein in particular catalyses the phosphorylation of the following substances:

$CH_2(OH)-C(CH_3)=C(OH)-CH_2-O-PO(OH)_2$,

$CH_2(OH)-C(CH_3)=C(OH)-CH_2-OH$,

$CH_2(OH)-CH(CH_3)-CO-CH_2-O-PO(OH)_2$,

$CH_2(OH)-CH(CH_3)-CO-CH_2OH$

$CH_2=C(CH_3)-CO-CH_2-O-PO(OH)_2$,

$CH_2=C(CH_3)-CO-CH_2-OH$,

$CH_2=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,

$CH_2=C(CH_3)-CH(OH)-CH_2-OH$,

$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-O-PO(OH)_2$,

$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-OH$

$CHO-CH(CH_3)-CH(OH)-CH_2-O-PO-(OH)_2$,

$CHO-CH(CH_3)-CH(OH)-CH_2-OH$,

$CH_2(OH)-C(OH)(CH_3)-CH=CH-O-PO(OH)_2$,

$CH_2(OH)-C(OH)(CH_3)-CH=CH-OH$

$CH(OH)=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,

$CH(OH)=C(CH_3)-CH(OH)-CH_2-OH$,

$(CH_3)_2HC-CO-CH_2-O-PO(OH)_2$,

$(CH_3)_2HC-CO-CH_2-O-H$,

$(CH_3)_2HC-CH(OH)-CH_2-O-PO(OH)_2$,

$(CH_3)_2HC-CH(OH)-CH_2-O-H$.

DOXP synthase catalyses the condensation of pyruvate and glyceraldehyde 3-phosphate to yield 1-deoxy-D-xylulose 5-phosphate and DOXP reductoisomerase catalyses the conversion of 1-deoxy-D-xylulose 5-phosphate into 2-C-methyl-D-erythritol 4-phosphate (*c.f.* Fig. 1).

The invention relates to the following DNA sequences:
DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 2 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included,

DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 4 or for an analogue or derivative of the polypeptide according to SEQ ID no. 4, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included,

and DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 6, in which one or more amino acids have been

deleted, added or replaced by other amino acids, wherein the catalytic function of the polypeptide is retained.

The genes and the gene products thereof (polypeptides) are shown with their primary structure and are assigned as follows:

SEQ ID no. 1: 1-deoxy-D-xylulose 5-phosphate reducto-isomerase gene

SEQ ID no. 2: 1-deoxy-D-xylulose 5-phosphate reducto-isomerase

SEQ ID no. 3: 1-deoxy-D-xylulose 5-phosphate synthase gene

SEQ ID no. 4: 1-deoxy-D-xylulose 5-phosphate synthase

SEQ ID no. 5: gcpE gene
SEQ ID no. 6: gcpE proteins.

The DNA sequences all originate from *Plasmodium falciparum*.

Apart from the DNA sequences stated in the sequence listing, suitable sequences are also those which, as a result of the degeneration of the genetic code, have another DNA sequence, but code for the same peptide or for an analogue or derivative of the polypeptide, in which one or more amino acids have been deleted, added or replaced by other amino acids.

The sequences according to the invention are suitable for the expression of genes in viruses, eukaryotes and prokaryotes which are responsible for isoprenoid biosynthesis in the 1-deoxy-D-xylulose pathway.

According to the invention, eukaryotes or eukaryotic cells include animal cells, plant cells, algae, yeasts, fungi, while prokaryotes or prokaryotic cells include bacteria, archaebacteria and eubacteria.

When a DNA sequence is incorporated into a genome on which the above-stated DNA sequence is located, expression of the above-described genes in viruses, eukaryotes and prokaryotes is enabled. The viruses, eukaryotes and prokaryotes transformed according to the invention are cultivated in a manner known *per se* and the isoprenoid formed during such cultivation is isolated and optionally purified. Not all isoprenoids need to be

isolated as in some case the isoprenoids are released directly into the ambient air.

The invention furthermore relates to a process for the production of transgenic viruses, eukaryotes and prokaryotes in order to modify the isoprenoid content, which process comprises the following steps.

a) Production of a DNA sequence with the following sub-sequences
   i) promoter which is active in viruses, eukaryotes and prokaryotes and ensures the formation of an RNA in the intended target tissue or target cells,
   ii) DNA sequence which codes for a polypeptide with the amino acid sequence shown in SEQ ID no. 2, 4 or 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, 4 or 6,
   iii) 5' and 3' untranslated sequence which enables or enhances expression of the stated genes in viruses, eukaryotes and prokaryotes,
b) transfer and incorporation of the DNA sequence into the genome of viruses, prokaryotic or eukaryotic cells with or without the use of a vector (for example plasmid, viral DNA).

The intact, whole plants may be regenerated from plant cells transformed in this manner.

The protein-coding sequences with the nucleotide sequences SEQ ID no. 1, SEQ ID no. 3 and SEQ ID no. 5 may be provided with a promoter which ensures transcription in certain organs or cells, which promoter is coupled in

sense orientation (3' end of the promoter to the 5' end of the coding sequence) to the sequence which codes the protein to be formed. A termination signal which determines termination of mRNA synthesis is attached to the 3' end of the coding sequence. In order to direct the protein which is to be expressed to certain subcellular compartments, such as chloroplasts, amyloplasts, mitochondria, vacuoles, cytosol or intercellular spaces, a further sequence which codes for a so-called signal sequence or a transit peptide may be inserted between the promoter and the coding sequence. In some cases, it is necessary to insert sequences which code for a signal at the COOH terminus of the protein. The sequence must be in the same reading frame as the coding sequence of the protein. A large number of cloning vectors is available in order to prepare for the introduction of the DNA sequences according to the invention into higher plants, which vectors contain a replication signal for *E. coli* and a marker which permits selection of the transformed cells. Depending upon the method by which desired genes are introduced into the plant, further DNA sequences may be required. If, for example, the Ti or Ri plasmid is used to transform the plant cells, at least one right border, but frequently the right border and left border of the Ti and Ri plasmid T-DNA must be inserted as a flanking region into the genes to be introduced. The use of T-DNA for transforming plant cells has been intensively investigated and comprehensively described in EP 120516; Hoekama in "The Binary Plant Vector System", Offset-drukkerij Kanters B.V. Alblasserdam (1985), chapter V; Fraley *et al.*, *Crit.Rev.Plant Sci.* 4, 1-46 and An *et al.* (1985) *EMBO J.* 4, 277-287. Once the introduced DNA has been incorporated into the genome, it is

generally stable and is also retained in the descendants of the originally transformed cells. It normally contains a selection marker, which imparts to the transformed plant cells resistance to a biocide or an antibiotic, such as kanamycin, G 418, bleomycin, hygromycin or phosphinotricin and others. The particular marker used is thus intended to allow selection of transformed cells from cells lacking the inserted DNA.

Many techniques are available for introducing DNA into a plant. These techniques include transformation with the assistance of agrobacteria, for example *Agrobacterium tumefaciens*, protoplast fusion, microinjection of DNA, electroporation, as well as ballistic methods and virus infection. Whole plants may then be regenerated from the transformed plant material in a suitable medium which may contain antibiotics or biocides for selection purposes. No particular requirements are placed upon the plasmids for injection and electroporation. However, if whole plants are to be regenerated from such transformed cells, a selectable marker gene must be present. The transformed cells grow in the plants in the conventional manner (McCormick *et al.* (1986), *Plant Cell Reports* 5, 81-84). The plants may be cultivated normally and be crossed with plants which have the same transformed genome or other genomes. The resultant individuals have the corresponding phenotypic properties.

The present invention also provides expression vectors which contain one or more of the DNA sequences according to the invention. Such expression vectors are obtained by providing the DNA sequences according to the invention with suitable functional regulation signals. Such

regulation signals are DNA sequences which are responsible for expression, for example promoters, operators, enhancers, ribosomal binding sites, and are recognised by the host organism.

Further regulation signals, which for example control replication or recombination of the recombinant DNA in the host organism, may optionally also be a constituent part of the expression vector.

The host organisms transformed with the DNA sequences or expression vectors according to the invention are also provided by the present invention.

Suitable host cells and organisms for expressing the enzymes according to the invention are those which comprise no intrinsic enzymes with the function of DOXP synthase, DOXP reductoisomerase or the gcpE protein. This is the case for archaebacteria, animals, fungi, slime moulds and some eubacteria. The absence of such intrinsic enzyme activity substantially facilitates detection and purification of the recombinant enzymes. As a consequence, it is also for the first time possible straightforwardly to measure, in crude extracts from the host cells, the activity and in particular the inhibition of the activity of the recombinant enzymes according to the invention by various chemicals and pharmaceuticals.

The enzymes according to the invention are advantageously then expressed in eukaryotic cells if post-translational modification and native folding of the polypeptide chain is to be achieved. Moreover, depending upon the expression system, it is ensured when expressing genomic

DNA sequences that introns are eliminated by splicing the DNA and the enzymes are produced in the polypeptide sequences characteristic to the parasites. Using recombinant DNA techniques, sequences coding for introns may be eliminated from or inserted for experimental purposes into the DNA sequences to be expressed.

The protein may be isolated from the host cell or the culture supernatant of the host cell using methods known to the person skilled in the art. *In vitro* reactivation of the enzymes may also be required.

In order to facilitate purification, the enzymes according to the invention or sub-sequences of the enzymes may be expressed as fusion proteins with various peptide chains. Oligo-histidine sequences and sequences derived from glutathione S-transferase, thioredoxin or calmodulin-binding peptides are particularly suitable for this purpose.

The enzymes according to the invention or sub-sequences of the enzymes may furthermore be expressed as fusion proteins with such peptide chains known to the person skilled in the art that the recombinant enzymes are transported into the extracellular medium or into certain compartments of the host cells. Both purification and investigation of the biological activity of the enzymes may consequently be facilitated.

When expressing the enzymes according to the invention, it may prove convenient to modify individual codons. Purposeful replacement of bases in the coding region may here also be advisable if the codons used in the

parasites differ from the codon use in the heterologous expression system, in order to ensure optimal synthesis of the protein.

The enzymes according to the invention may furthermore be obtained under standardised conditions by *in vitro* translation by methods known to the person skilled in the art. Systems suitable for this purpose are rabbit reticulocyte and wheat germ extracts and bacterial lysates. *In vitro* transcribed mRNA may also be translated into *Xenopus* oocytes.

Oligo- and polypeptides, the sequences of which are derived from the peptide sequence of the enzymes according to the invention, may be obtained by chemical synthesis. Given appropriate selection of the sequences, such peptides have properties which are characteristic of the enzymes according to the invention. Such peptides may be produced in large quantities and are particularly suitable for investigating the kinetics of enzyme activity, regulation of enzyme activity, the three-dimensional structure of the enzymes, inhibition of enzyme activity by various chemicals and pharmaceuticals and the binding geometry and binding affinity of various ligands.

DNA with the nucleotides from sequences SEQ ID no. 1, 3 and 5 are preferably used for the recombinant production of the enzymes according to the invention.

The invention accordingly moreover relates to a process for screening for compounds which inhibit the deoxy-D-xylulose phosphate metabolic pathway. According to this

process, a host organism, which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or homologues thereof, is provided, as is a compound which is suspected to have antimicrobial, antiparasitic, antibacterial, antiviral and antimycotic action in humans and animals or an antimicrobial, antiviral, bactericidal, herbicidal or fungicidal activity in plants. The host organism is then brought into contact with the compound and the activity of the compound determined.

The present invention also provides methods for determining the enzymatic activity of the gcpE protein. Said activity may be determined using known methods. Determination is performed by detecting the phosphorylation of a sugar or of a phosphorus sugar or of a precursor of isoprenoid biosynthesis, in particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erytritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate. The present invention also provides the use of this measurement method for identifying substances which inhibit the activity of the particular enzymes.

The enzymatic activity of DOXP synthase and DOXP reductoisomerase may be detected in a single step by determining the conversion of glyceraldehyde 3-phosphate into 2-C-methylerythritol 4-phosphate.

Determination of the activities of DOXP synthase and DOXP reductoisomerase proceeds analogously. Fluorimetric methods described by Querol *et al.* are also suitable for determining DOXP synthase activity (Querol *et al.*, abstracts, 4th European Symposium on Plant Isoprenoids, Barcelona, 21-23 April 1999).

Claims

1. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 2 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included.

2. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 4 or for an analogue or derivative of the polypeptide according to SEQ ID no. 4, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included.

3. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 6, in which one or more amino acids have been deleted, added or replaced by other amino acids wherein the catalytic function of the polypeptide is retained.

4. DNA sequence according to one of claims 1 to 3, characterised in that it also comprises functional regulation signals, in particular promoters, operators, enhancers, ribosomal binding sites.

5. DNA sequence with the following sub-sequences

i) promoter which is active in viruses, eukaryotes and prokaryotes and ensures the formation of an RNA in the intended target tissue or target cells,

ii) DNA sequences according to one of claims 1 to 3,

iii) 3' untranslated sequence which, in viruses, eukaryotes and prokaryotes, results in the addition of poly(A) residues onto the 3' end of the RNA.

6. Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, characterised in that a DNA sequence according to claim 4 or 5 is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.

7. Transgenic systems, in particular plants and plant cells which contain one or more DNA sequences according to claims 1 to 5 as "foreign" or "additional" DNA, which sequences are expressed.

8. Expression vector containing one or more DNA sequences according to claims 1 to 5.

9. Protein which is involved in the 1-deoxy-D-xylulose 5-phosphate metabolic pathway and a) is coded by DNA sequences SEQ ID no. 1, 3 or 5 or b) is coded by DNA sequences which hybridise with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein.

10. Protein according to claim 9, obtainable from the culture supernatants of parasites or from the disrupted parasites and purification by chromatographic and electrophoretic methods.

11. Protein according to one of claims 9 and 10, characterised in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which hybridise with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would hybridise without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.

12. Protein according to one of the preceding claims, characterised in that it comprises the amino acid sequences SEQ ID no. 2, 4 or 6.

13. Process for determining the enzymatic activity of the gcpE protein, characterised in that phosphorylation of a sugar or of a phosphorus sugar or of a precursor of isoprenoid biosynthesis, in

particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erytritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate, and of phosphate and alcohol precursors, is detected.

14. Process according to claim 13, characterised in that phosphorylation of the following phosphates or alcohols is detected:

$CH_2(OH)-C(CH_3)=C(OH)-CH_2-O-PO(OH)_2$,

$CH_2(OH)-C(CH_3)=C(OH)-CH_2-OH$,

$CH_2(OH)-CH(CH_3)-CO-CH_2-O-PO(OH)_2$,

$CH_2(OH)-CH(CH_3)-CO-CH_2OH$

$CH_2=C(CH_3)-CO-CH_2-O-PO(OH)_2$,

$CH_2=C(CH_3)-CO-CH_2-OH$,

$CH_2=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,

$CH_2=C(CH_3)-CH(OH)-CH_2-OH$,

$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-O-PO(OH)_2$,

$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-OH$

$CHO-CH(CH_3)-CH(OH)-CH_2-O-PO-(OH)_2$,

$CHO-CH(CH_3)-CH(OH)-CH_2-OH$,

$CH_2(OH)-C(OH)(CH_3)-CH=CH-O-PO(OH)_2$,

$CH_2(OH)-C(OH)(CH_3)-CH=CH-OH$

$CH(OH)=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,

$CH(OH)=C(CH_3)-CH(OH)-CH_2-OH$,

$(CH_3)_2HC-CO-CH_2-O-PO(OH)_2$,

$(CH_3)_2HC-CO-CH_2-O-H$,

$(CH_3)_2HC-CH(OH)-CH_2-O-PO(OH)_2$,

$(CH_3)_2HC-CH(OH)-CH_2-O-H$.

15. Process for the combined determination of the enzymatic activity of DOXP synthase and of DOXP reductase, characterised in that the conversion of glyceraldehyde 3-phosphate into 2-C-methylerythritol 4-phosphate is detected.

16. Process for screening a compound for the treatment of infectious processes in humans and animals, wherein the process comprises:

a) provision of a host cell which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or analogues thereof, and moreover of a compound suspected to have antimycotic, antibiotic, antiparasitic or antiviral action in humans and animals,

b) bringing the host cell into contact with the compound and

c) determining the antimicrobial, antimycotic, antibiotic, antiparasitic or antiviral action of the compound.

17. Process for screening for compounds for treating plants, wherein the process comprises:

a) provision of a host cell which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or analogues thereof, and moreover of a compound suspected to have antimicrobial,

antiviral, antiparasitic, bactericidal, fungicidal or herbicidal action in plants,

b) bringing the host cell into contact with the compound and

c) determining the antimicrobial, antiviral, antiparasitic, bactericidal, fungicidal or herbicidal action of the compound.

18. Use of DNA according to one of claims 1 to 5 or of proteins according to one of claims 9 to 12 or of transgenic systems according to claim 7 for the prevention or treatment of diseases in humans and animals.

SEQUENCE LISTING

<110> Jomaa, Hassan

<120> Genes of the 1-deoxy-D-xylulose biosynthesis pathway

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<141> 1999-09-22

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Ile Arg Glu Cys Asn Lys Ile Glu Asn Val Phe Asn Val Lys Ala Leu
            100                 105                 110

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            180                 185                 190

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385                 390                 395                 400

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Gln Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn
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                420                 425                 430

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Leu Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe
            435                 440                 445
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tta ttt ttt att gta aat ata aca gga ggt cat ttt tcc tct gtt tta   1514
Leu Phe Phe Ile Val Asn Ile Thr Gly Gly His Phe Ser Ser Val Leu
        450                 455                 460

agc tct tta gaa att caa tta tta tta ttg tat att ttt aat caa cca   1562
Ser Ser Leu Glu Ile Gln Leu Leu Leu Leu Tyr Ile Phe Asn Gln Pro
    465                 470                 475

tat gat aat gtt ata tat gat ata gga cat caa gca tat gta cat aag   1610
Tyr Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys
480                 485                 490                 495

ata ttg acc gga aga aaa cta tta ttt cta tca tta aga aat aaa aaa   1658
Ile Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys
                500                 505                 510

ggt att agt gga ttc cta aat att ttt gaa agt att tat gat aaa ttt   1706
Gly Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe
            515                 520                 525

ggg gct ggt cac agt tcc act tca tta agt gct ata caa gga tat tat   1754
Gly Ala Gly His Ser Ser Thr Ser Leu Ser Ala Ile Gln Gly Tyr Tyr
        530                 535                 540

gaa gcc gag tgg caa gtg aag aat aaa gaa aaa tat gga aat gga gat   1802
Glu Ala Glu Trp Gln Val Lys Asn Lys Glu Lys Tyr Gly Asn Gly Asp
    545                 550                 555

ata gaa ata agt gat aac gca aat gtc acg aat aat gaa agg ata ttt   1850
Ile Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe
560                 565                 570                 575

caa aaa gga ata cac aat gat aat aat att aac aat aat att aat aat   1898
Gln Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn
                580                 585                 590

aat aat tat atc aat cct tca gat gtg gta gga aga gaa aat acg aat   1946
Asn Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn
            595                 600                 605

gta cca aat gta cga aat gat aac cat aac gtg gat aaa gta cac att   1994
Val Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile
        610                 615                 620

gct att ata gga gat ggt ggt tta aca ggt gga atg gca tta gaa gcg   2042
Ala Ile Ile Gly Asp Gly Gly Leu Thr Gly Gly Met Ala Leu Glu Ala
    625                 630                 635

tta aat tat att tca ttc ttg aat tct aaa att tta att att tat aat   2090
Leu Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn
640                 645                 650                 655

gat aac gga caa gtt tct tta cca aca aat gcc gta agt ata tca ggt   2138
Asp Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly
                660                 665                 670
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aat aga cct ata ggt tct ata tca gat cat tta cat tat ttt gtt tct   2186
Asn Arg Pro Ile Gly Ser Ile Ser Asp His Leu His Tyr Phe Val Ser
            675                 680                 685

aat ata gaa gca aat gct ggt gat aat aaa tta tcg aaa aat gca aaa   2234
Asn Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys
        690                 695                 700

gag aat aac att ttt gaa aat ttg aat tat gat tat att ggt gtt gtg   2282
Glu Asn Asn Ile Phe Glu Asn Leu Asn Tyr Asp Tyr Ile Gly Val Val
    705                 710                 715

aat ggt aat aat aca gaa gag ctc ttt aaa gta tta aat aat ata aaa   2330
Asn Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys
720                 725                 730                 735

gaa aat aaa tta aaa aga gct act gtt ctt cat gta cgt aca aaa aaa   2378
Glu Asn Lys Leu Lys Arg Ala Thr Val Leu His Val Arg Thr Lys Lys
                740                 745                 750

tcg aat gat ttt ata aat tca aag agt cca ata agt ata ttg cac tct   2426
Ser Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser
            755                 760                 765

ata aag aaa aat gag att ttc cct ttc gat acc act ata tta aat gga   2474
Ile Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly
        770                 775                 780

aat att cat aag gag aac aag ata gaa gaa gag aaa aat gtg tct tca   2522
Asn Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser
    785                 790                 795

tct aca aag tat gat gta aat aat aag aat aat aaa aat aat gat aat   2570
Ser Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn
800                 805                 810                 815

agt gaa att ata aaa tat gaa gat atg ttt tca aaa gag acg ttc aca   2618
Ser Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr
                820                 825                 830

gat ata tat aca aat gaa atg tta aaa tat tta aag aaa gat aga aat   2666
Asp Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn
            835                 840                 845

ata ata ttc cta tct ccc gct atg tta gga gga tca gga ttg gtt aaa   2714
Ile Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys
        850                 855                 860

att agt gag cgt tat cca aat aat gta tat gat gta ggt ata gca gaa   2762
Ile Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu
    865                 870                 875

caa cat tct gta act ttc gca gca gct atg gca atg aat aag aaa tta   2810
Gln His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu
880                 885                 890                 895
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aaa ata caa tta tgt ata tat tcg acc ttt tta caa aga gca tat gat   2858
Lys Ile Gln Leu Cys Ile Tyr Ser Thr Phe Leu Gln Arg Ala Tyr Asp
                900                 905                 910

caa att ata cat gat ctt aat tta caa aat ata cct tta aag gtt ata   2906
Gln Ile Ile His Asp Leu Asn Leu Gln Asn Ile Pro Leu Lys Val Ile
            915                 920                 925

att gga aga agt gga tta gta gga gag gat ggg gca aca cat caa ggt   2954
Ile Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly
        930                 935                 940

ata tat gat tta tct tat ctt ggg aca ctt aac aat gca tat ata ata   3002
Ile Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile
    945                 950                 955

tct cca agt aat caa gtt gat ttg aaa aga gct ctt agg ttt gct tat   3050
Ser Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr
960                 965                 970                 975

tta gat aag gac cat tct gtg tat ata cgt ata ccc aga atg aac ata   3098
Leu Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile
                980                 985                 990

tta agt gat aag tac atg aaa gga tat ttg aac att cat atg aaa aat   3146
Leu Ser Asp Lys Tyr Met Lys Gly Tyr Leu Asn Ile His Met Lys Asn
            995                1000                1005

gag agc aaa aat atc gat gta aac gtg gat ata aac gat gat gta gat   3194
Glu Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp
       1010                1015                1020

aaa tat agt gaa gaa tat atg gac gat gat aat ttt ata aaa tcg ttt   3242
Lys Tyr Ser Glu Glu Tyr Met Asp Asp Asp Asn Phe Ile Lys Ser Phe
   1025                1030                1035

att gga aaa tct aga att att aaa atg gat aat gaa aat aat aat aca   3290
Ile Gly Lys Ser Arg Ile Ile Lys Met Asp Asn Glu Asn Asn Asn Thr
1040                1045                1050                1055

aat gaa cat tat tca agc aga gga gat aca cag aca aaa aaa aaa aaa   3338
Asn Glu His Tyr Ser Ser Arg Gly Asp Thr Gln Thr Lys Lys Lys Lys
               1060                1065                1070

gtt tgt atc ttt aac atg ggt agt atg ctt ttt aat gta att aat gct   3386
Val Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala
           1075                1080                1085

ata aaa gaa att gaa aaa gaa caa tat att tca cat aat tat tct ttt   3434
Ile Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe
       1090                1095                1100

tca att gtt gat atg ata ttt tta aat cct tta gat aaa aat atg ata   3482
Ser Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile
   1105                1110                1115
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gat cat gta ata aaa caa aat aaa cat caa tat tta att act tat gaa   3530
Asp His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu
1120                1125                1130                1135

gat aat act ata ggt ggt ttt tct aca cat ttc aat aat tat tta ata   3578
Asp Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile
                1140                1145                1150

gaa aat aat tat att aca aaa cat aac tta tat gtt cat aat att tat   3626
Glu Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr
            1155                1160                1165

tta tct aat gag cca att gaa cat gca tct ttt aag gat caa caa gaa   3674
Leu Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu
        1170                1175                1180

gtc gtc aaa atg gat aaa tgt agt ctt gtc aat aga att aaa aat tat   3722
Val Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr
    1185                1190                1195

ctt aaa aat aat cct aca tgatgtaaga taaatatata tttctaaaat          3770
Leu Lys Asn Asn Pro Thr
1200                1205

tatttttttt ttatacttta atgtgtacaa taaaatatat atctaaatat attttatttg 3830

tacgcttttt ttttttttt tttaattgtt atttttgtat at                     3872


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            20                  25                  30

Asn Gln Ile Lys Thr Glu Lys Ile Tyr Ile Lys Lys Leu Asn Arg Leu
        35                  40                  45

Ser Arg Lys Asn Ser Leu Cys Ser Ser Lys Asn Lys Ile Ala Cys Leu
    50                  55                  60

Phe Asp Ile Gly Asn Asp Asp Asn Arg Asn Thr Thr Tyr Gly Tyr Asn
65                  70                  75                  80

Val Asn Val Lys Asn Asp Asp Ile Asn Ser Leu Leu Lys Asn Asn Tyr
                85                  90                  95

Ser Asn Lys Leu Tyr Met Asp Lys Arg Lys Asn Ile Asn Asn Val Ile
            100                 105                 110

Ser Thr Asn Lys Ile Ser Gly Ser Ile Ser Asn Ile Cys Ser Arg Asn
        115                 120                 125
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Gln Lys Glu Asn Glu Gln Lys Arg Asn Lys Gln Arg Cys Leu Thr Gln
130 135 140

Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn Asp
145 150 155 160

Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn Tyr
165 170 175

Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn Phe
180 185 190

Phe Tyr Cys Lys Glu Lys Lys Leu Ser Phe Leu His Lys Ala Tyr Lys
195 200 205

Lys Lys Asn Cys Thr Phe Gln Asn Tyr Ser Leu Lys Arg Lys Ser Asn
210 215 220

Arg Asp Ser His Lys Leu Phe Ser Gly Glu Phe Asp Asp Tyr Thr Asn
225 230 235 240

Asn Asn Ala Leu Tyr Glu Ser Glu Lys Lys Glu Tyr Ile Thr Leu Asn
245 250 255

Asn Asn Asn Lys Asn Asn Asn Asn Lys Asn Asn Asp Asn Lys Asn Asn
260 265 270

Asp Asn Asn Asp Tyr Asn Asn Asn Asn Ser Cys Asn Asn Leu Gly Glu
275 280 285

Arg Ser Asn His Tyr Asp Asn Tyr Gly Gly Asp Asn Asn Asn Pro Cys
290 295 300

Asn Asn Asn Asn Asp Lys Tyr Asp Ile Gly Lys Tyr Phe Lys Gln Ile
305 310 315 320

Asn Thr Phe Ile Asn Ile Asp Glu Tyr Lys Thr Ile Tyr Gly Asp Glu
325 330 335

Ile Tyr Lys Glu Ile Tyr Glu Leu Tyr Val Glu Arg Asn Ile Pro Glu
340 345 350

Tyr Tyr Glu Arg Lys Tyr Phe Ser Glu Asp Ile Lys Lys Ser Val Leu
355 360 365

Phe Asp Ile Asp Lys Tyr Asn Asp Val Glu Phe Glu Lys Ala Ile Lys
370 375 380

Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn Thr
385 390 395 400

Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His Tyr
405 410 415

Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys Leu
420 425 430

Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe Leu
435 440 445

Phe Phe Ile Val Asn Ile Thr Gly Gly His Phe Ser Ser Val Leu Ser
450 455 460

Ser Leu Glu Ile Gln Leu Leu Leu Leu Tyr Ile Phe Asn Gln Pro Tyr
465 470 475 480

Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys Ile
485 490 495

Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys Gly
500 505 510

Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe Gly
515 520 525

Ala Gly His Ser Ser Thr Ser Leu Ser Ala Ile Gln Gly Tyr Tyr Glu
530 535 540

Ala Glu Trp Gln Val Lys Asn Lys Glu Lys Tyr Gly Asn Gly Asp Ile
545 550 555 560

Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe Gln
565 570 575

Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn Asn
580 585 590

Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn Val
595 600 605

Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile Ala
610 615 620

Ile Ile Gly Asp Gly Gly Leu Thr Gly Gly Met Ala Leu Glu Ala Leu
625 630 635 640

Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn Asp
645 650 655

Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly Asn
660 665 670

Arg Pro Ile Gly Ser Ile Ser Asp His Leu His Tyr Phe Val Ser Asn
675 680 685

Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys Glu
690 695 700

Asn Asn Ile Phe Glu Asn Leu Asn Tyr Asp Tyr Ile Gly Val Val Asn
705 710 715 720

Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys Glu
725 730 735

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Asn Lys Leu Lys Arg Ala Thr Val Leu His Val Arg Thr Lys Lys Ser
            740                 745                 750

Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser Ile
        755                 760                 765

Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly Asn
    770                 775                 780

Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser Ser
785                 790                 795                 800

Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn Ser
                805                 810                 815

Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr Asp
            820                 825                 830

Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn Ile
        835                 840                 845

Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys Ile
    850                 855                 860

Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu Gln
865                 870                 875                 880

His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu Lys
                885                 890                 895

Ile Gln Leu Cys Ile Tyr Ser Thr Phe Leu Gln Arg Ala Tyr Asp Gln
            900                 905                 910

Ile Ile His Asp Leu Asn Leu Gln Asn Ile Pro Leu Lys Val Ile Ile
        915                 920                 925

Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly Ile
    930                 935                 940

Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile Ser
945                 950                 955                 960

Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr Leu
                965                 970                 975

Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile Leu
            980                 985                 990

Ser Asp Lys Tyr Met Lys Gly Tyr Leu Asn Ile His Met Lys Asn Glu
        995                1000                1005

Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp Lys
   1010                1015                1020

Tyr Ser Glu Glu Tyr Met Asp Asp Asp Asn Phe Ile Lys Ser Phe Ile
025                1030                1035                1040
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Gly Lys Ser Arg Ile Ile Lys Met Asp Asn Glu Asn Asn Asn Thr Asn
                1045                1050                1055

Glu His Tyr Ser Ser Arg Gly Asp Thr Gln Thr Lys Lys Lys Lys Val
            1060                1065                1070

Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala Ile
        1075                1080                1085

Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe Ser
    1090                1095                1100

Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile Asp
105                 1110                1115                1120

His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu Asp
                1125                1130                1135

Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile Glu
            1140                1145                1150

Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr Leu
        1155                1160                1165

Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu Val
    1170                1175                1180

Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr Leu
185                 1190                1195                1200

Lys Asn Asn Pro Thr
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atacatctcc aacatataaa tattattttt tattattatt ttttttttt tttttcataa 180

tgcctgaata accacaaa atg agt tat ata aaa aga ctg att ctt ttt atg 231
Met Ser Tyr Ile Lys Arg Leu Ile Leu Phe Met
1 5 10

tta ctg ttt tat tct cat gta aaa att aaa aaa tta ttt att aaa att 279
Leu Leu Phe Tyr Ser His Val Lys Ile Lys Lys Leu Phe Ile Lys Ile
15 20 25

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tct aat gta aac ata ttt ttt gca gaa gca aag aaa aat gga aaa aag   327
Ser Asn Val Asn Ile Phe Phe Ala Glu Ala Lys Lys Asn Gly Lys Lys
          30                  35                  40

gaa ttc ttt ctt ttt tta cta aat ata aaa aaa aat agc caa cag aaa   375
Glu Phe Phe Leu Phe Leu Leu Asn Ile Lys Lys Asn Ser Gln Gln Lys
     45                  50                  55

aaa act tat cat att acc aaa agg aat acc ata aat aaa agt gat ttt   423
Lys Thr Tyr His Ile Thr Lys Arg Asn Thr Ile Asn Lys Ser Asp Phe
 60                  65                  70                  75

tta tat tct tta cta aat gaa gaa ggg aat tct tca aaa aag gaa tat   471
Leu Tyr Ser Leu Leu Asn Glu Glu Gly Asn Ser Ser Lys Lys Glu Tyr
                 80                  85                  90

aaa aat tta aaa gat gaa gaa aaa tat aat atc ata caa aat ata aaa   519
Lys Asn Leu Lys Asp Glu Glu Lys Tyr Asn Ile Ile Gln Asn Ile Lys
             95                 100                 105

aaa tat tgt gaa tgt act aaa aaa tat aaa agg ctc cca aca cga gaa   567
Lys Tyr Cys Glu Cys Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu
         110                 115                 120

gta gtt att gga aat gtt aaa att gga gga aat aat aaa ata gct att   615
Val Val Ile Gly Asn Val Lys Ile Gly Gly Asn Asn Lys Ile Ala Ile
     125                 130                 135

caa act atg gct agc tgt gat aca aga aat gta gaa gaa tgt gta tat   663
Gln Thr Met Ala Ser Cys Asp Thr Arg Asn Val Glu Glu Cys Val Tyr
140                 145                 150                 155

caa att aga aaa tgt aaa gat ttg ggt gct gac att gta agg ttg act   711
Gln Ile Arg Lys Cys Lys Asp Leu Gly Ala Asp Ile Val Arg Leu Thr
                160                 165                 170

gtt caa gga gtt caa gaa gca caa gct agt tat cat att aaa gaa aaa   759
Val Gln Gly Val Gln Glu Ala Gln Ala Ser Tyr His Ile Lys Glu Lys
            175                 180                 185

tta tta tct gaa aat gta aat atc cca tta gta gca gat att cat ttt   807
Leu Leu Ser Glu Asn Val Asn Ile Pro Leu Val Ala Asp Ile His Phe
        190                 195                 200

aat cct aaa ata gct tta atg gca gct gat gtg ttt gaa aaa att cga   855
Asn Pro Lys Ile Ala Leu Met Ala Ala Asp Val Phe Glu Lys Ile Arg
    205                 210                 215

gtg aat cca gga aat tat gtt gat gga aga aaa aaa tgg ata gat aaa   903
Val Asn Pro Gly Asn Tyr Val Asp Gly Arg Lys Lys Trp Ile Asp Lys
220                 225                 230                 235

gtt tat aaa act aaa gaa gaa ttt gat gaa ggg aaa tta ttt ata aaa   951
Val Tyr Lys Thr Lys Glu Glu Phe Asp Glu Gly Lys Leu Phe Ile Lys
                240                 245                 250
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gaa aaa ttt gta cca tta att gaa aaa tgt aaa aga tta aat aga gca   999
Glu Lys Phe Val Pro Leu Ile Glu Lys Cys Lys Arg Leu Asn Arg Ala
            255                 260                 265

ata aga att gga aca aat cat gga tcc ctt tca tct cga gta tta tca  1047
Ile Arg Ile Gly Thr Asn His Gly Ser Leu Ser Ser Arg Val Leu Ser
        270                 275                 280

tat tat gga gat aca cca tta ggt atg gta gaa tcg gct ttt gag ttt  1095
Tyr Tyr Gly Asp Thr Pro Leu Gly Met Val Glu Ser Ala Phe Glu Phe
    285                 290                 295

tct gat tta tgt att gaa aac aat ttt tac aat ctt gtt ttt tct atg  1143
Ser Asp Leu Cys Ile Glu Asn Asn Phe Tyr Asn Leu Val Phe Ser Met
300                 305                 310                 315

aaa gct tct aat gct tat gtt atg ata caa tct tat aga tta tta gta  1191
Lys Ala Ser Asn Ala Tyr Val Met Ile Gln Ser Tyr Arg Leu Leu Val
                320                 325                 330

tct aaa caa tat gaa aga aat atg atg ttc cct ata cat tta gga gtt  1239
Ser Lys Gln Tyr Glu Arg Asn Met Met Phe Pro Ile His Leu Gly Val
            335                 340                 345

aca gaa gca gga ttt ggt gat aat gga aga ata aaa tct tat tta ggt  1287
Thr Glu Ala Gly Phe Gly Asp Asn Gly Arg Ile Lys Ser Tyr Leu Gly
        350                 355                 360

ata gga tct tta tta tat gat ggt ata gga gat acc att cgt ata tcc  1335
Ile Gly Ser Leu Leu Tyr Asp Gly Ile Gly Asp Thr Ile Arg Ile Ser
    365                 370                 375

tta aca gaa gat cct tgg gaa gag tta act cct tgt aaa aaa tta gtt  1383
Leu Thr Glu Asp Pro Trp Glu Glu Leu Thr Pro Cys Lys Lys Leu Val
380                 385                 390                 395

gaa aat tta aag aaa aga ata ttt tat aat gaa aat ttt aaa gaa gat  1431
Glu Asn Leu Lys Lys Arg Ile Phe Tyr Asn Glu Asn Phe Lys Glu Asp
                400                 405                 410

aat gaa tta aaa aat aat gaa atg gat acc aaa aat cta tta aat ttt  1479
Asn Glu Leu Lys Asn Asn Glu Met Asp Thr Lys Asn Leu Leu Asn Phe
            415                 420                 425

gaa gaa aat tat cga aat ttt aat aat ata aaa aaa aga aat gta gaa  1527
Glu Glu Asn Tyr Arg Asn Phe Asn Asn Ile Lys Lys Arg Asn Val Glu
        430                 435                 440

aaa aat aat aat gta tta cat gaa gag tgc act ata ggt aat gta gta  1575
Lys Asn Asn Asn Val Leu His Glu Glu Cys Thr Ile Gly Asn Val Val
    445                 450                 455

acc ata aaa gag tta gaa gat tct ctg caa att ttt aaa gat tta aat  1623
Thr Ile Lys Glu Leu Glu Asp Ser Leu Gln Ile Phe Lys Asp Leu Asn
460                 465                 470                 475
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tta gaa gta gat tca aat gga aat ttg aaa aag gga gcc aaa aca act   1671
Leu Glu Val Asp Ser Asn Gly Asn Leu Lys Lys Gly Ala Lys Thr Thr
                480                 485                 490

gat atg gtt att ata aat gat ttt cat aat ata aca aat tta gga aaa   1719
Asp Met Val Ile Ile Asn Asp Phe His Asn Ile Thr Asn Leu Gly Lys
            495                 500                 505

aaa act gtg gat aaa tta atg caa gtg gga att aat ata gta gtt caa   1767
Lys Thr Val Asp Lys Leu Met Gln Val Gly Ile Asn Ile Val Val Gln
        510                 515                 520

tat gaa cca cat aat ata gaa ttt ata gaa aaa atg gaa cca aat aat   1815
Tyr Glu Pro His Asn Ile Glu Phe Ile Glu Lys Met Glu Pro Asn Asn
    525                 530                 535

gat aat aat aat aat aat aat aat aat aat aat ata tta ttt tat gtg gat   1863
Asp Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Ile Leu Phe Tyr Val Asp
540                 545                 550                 555

ata aaa aat att atg aac agt tca gaa aaa aat att aaa tta agt aat   1911
Ile Lys Asn Ile Met Asn Ser Ser Glu Lys Asn Ile Lys Leu Ser Asn
                560                 565                 570

tct aaa gga tat gga tta att tta aac gga aaa gaa gat ata caa acc   1959
Ser Lys Gly Tyr Gly Leu Ile Leu Asn Gly Lys Glu Asp Ile Gln Thr
            575                 580                 585

ata aaa aaa ata aaa gaa tta aat cgt cgt cct tta ttc att cta tta   2007
Ile Lys Lys Ile Lys Glu Leu Asn Arg Arg Pro Leu Phe Ile Leu Leu
        590                 595                 600

aaa tca gat aac ata tat gaa cat gta tta ata acc aga aga att aat   2055
Lys Ser Asp Asn Ile Tyr Glu His Val Leu Ile Thr Arg Arg Ile Asn
    605                 610                 615

gaa ctt tta caa tcc tta aat ata aat ata cct tat ata cat tat gtt   2103
Glu Leu Leu Gln Ser Leu Asn Ile Asn Ile Pro Tyr Ile His Tyr Val
620                 625                 630                 635

gat att aat tca aac aat tat gat gat ata tta gtt aat tca aca tta   2151
Asp Ile Asn Ser Asn Asn Tyr Asp Asp Ile Leu Val Asn Ser Thr Leu
                640                 645                 650

tat gca gga agt tgt ttg atg gat tta atg ggg gat ggt ctt att gtt   2199
Tyr Ala Gly Ser Cys Leu Met Asp Leu Met Gly Asp Gly Leu Ile Val
            655                 660                 665

aac gta act aat gat gtt ctt aca aat aaa aaa aag ata gaa aca aaa   2247
Asn Val Thr Asn Asp Val Leu Thr Asn Lys Lys Lys Ile Glu Thr Lys
        670                 675                 680

tat gat gaa aaa gaa gaa gta gag gaa gag gga aac aat aaa gat att   2295
Tyr Asp Glu Lys Glu Glu Val Glu Glu Glu Gly Asn Asn Lys Asp Ile
    685                 690                 695
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cat aga ctt ttg agc aga gtt gca tta aat tca ttt tta aca tta aat   2343
His Arg Leu Leu Ser Arg Val Ala Leu Asn Ser Phe Leu Thr Leu Asn
700                 705                 710                 715

att tta caa gat aca aga ata cgt tta ttt aaa aca gat tat ata gcc   2391
Ile Leu Gln Asp Thr Arg Ile Arg Leu Phe Lys Thr Asp Tyr Ile Ala
                720                 725                 730

tgc cca tct tgt gga aga act tta ttt aat ata caa gaa act act aaa   2439
Cys Pro Ser Cys Gly Arg Thr Leu Phe Asn Ile Gln Glu Thr Thr Lys
            735                 740                 745

aaa att atg aaa tta aca ggg cac tta aaa ggc gtt aaa att gca gtc   2487
Lys Ile Met Lys Leu Thr Gly His Leu Lys Gly Val Lys Ile Ala Val
        750                 755                 760

atg gga tgt att gtt aat ggt ata gga gaa atg gca gat gca cat ttt   2535
Met Gly Cys Ile Val Asn Gly Ile Gly Glu Met Ala Asp Ala His Phe
    765                 770                 775

ggt tat gtt ggt agt gca cct aaa aaa att gat tta tat tat ggt aaa   2583
Gly Tyr Val Gly Ser Ala Pro Lys Lys Ile Asp Leu Tyr Tyr Gly Lys
780                 785                 790                 795

gag tta gta gaa aga aat ata cct gag gaa gaa gct tgt gat aaa ttg   2631
Glu Leu Val Glu Arg Asn Ile Pro Glu Glu Glu Ala Cys Asp Lys Leu
                800                 805                 810

ata gaa tta att aaa aaa cat aac aaa tgg aaa gat cca taaattgaat    2680
Ile Glu Leu Ile Lys Lys His Asn Lys Trp Lys Asp Pro
            815                 820

atggacaagt atttatttat ttatttatct tatatataat atattataaa tttttcgatg 2740

tatttttcct tttaaaattt tatttttttt ttatttttt ttttgaagta atatttataa 2800

tgcatacata atattaaaat gtgtattata taataatatc attttattgt tattttaaaa 2860

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His Val Lys Ile Lys Lys Leu Phe Ile Lys Ile Ser Asn Val Asn Ile
            20                  25                  30

Phe Phe Ala Glu Ala Lys Lys Asn Gly Lys Lys Glu Phe Phe Leu Phe
        35                  40                  45

Leu Leu Asn Ile Lys Lys Asn Ser Gln Gln Lys Lys Thr Tyr His Ile
    50                  55                  60

Thr Lys Arg Asn Thr Ile Asn Lys Ser Asp Phe Leu Tyr Ser Leu Leu
65                  70                  75                  80

Asn Glu Glu Gly Asn Ser Ser Lys Lys Glu Tyr Lys Asn Leu Lys Asp
                85                  90                  95

Glu Glu Lys Tyr Asn Ile Ile Gln Asn Ile Lys Lys Tyr Cys Glu Cys
            100                 105                 110

Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu Val Val Ile Gly Asn
        115                 120                 125

Val Lys Ile Gly Gly Asn Asn Lys Ile Ala Ile Gln Thr Met Ala Ser
    130                 135                 140

Cys Asp Thr Arg Asn Val Glu Glu Cys Val Tyr Gln Ile Arg Lys Cys
145                 150                 155                 160

Lys Asp Leu Gly Ala Asp Ile Val Arg Leu Thr Val Gln Gly Val Gln
                165                 170                 175

Glu Ala Gln Ala Ser Tyr His Ile Lys Glu Lys Leu Leu Ser Glu Asn
            180                 185                 190

Val Asn Ile Pro Leu Val Ala Asp Ile His Phe Asn Pro Lys Ile Ala
        195                 200                 205

Leu Met Ala Ala Asp Val Phe Glu Lys Ile Arg Val Asn Pro Gly Asn
    210                 215                 220

Tyr Val Asp Gly Arg Lys Lys Trp Ile Asp Lys Val Tyr Lys Thr Lys
225                 230                 235                 240

Glu Glu Phe Asp Glu Gly Lys Leu Phe Ile Lys Glu Lys Phe Val Pro
                245                 250                 255

Leu Ile Glu Lys Cys Lys Arg Leu Asn Arg Ala Ile Arg Ile Gly Thr
            260                 265                 270

Asn His Gly Ser Leu Ser Ser Arg Val Leu Ser Tyr Tyr Gly Asp Thr
        275                 280                 285

Pro Leu Gly Met Val Glu Ser Ala Phe Glu Phe Ser Asp Leu Cys Ile
    290                 295                 300

Glu Asn Asn Phe Tyr Asn Leu Val Phe Ser Met Lys Ala Ser Asn Ala
305                 310                 315                 320

Tyr Val Met Ile Gln Ser Tyr Arg Leu Leu Val Ser Lys Gln Tyr Glu
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                 325                 330                 335

Arg Asn Met Met Phe Pro Ile His Leu Gly Val Thr Glu Ala Gly Phe
            340                 345                 350

Gly Asp Asn Gly Arg Ile Lys Ser Tyr Leu Gly Ile Gly Ser Leu Leu
        355                 360                 365

Tyr Asp Gly Ile Gly Asp Thr Ile Arg Ile Ser Leu Thr Glu Asp Pro
    370                 375                 380

Trp Glu Glu Leu Thr Pro Cys Lys Lys Leu Val Glu Asn Leu Lys Lys
385                 390                 395                 400

Arg Ile Phe Tyr Asn Glu Asn Phe Lys Glu Asp Asn Glu Leu Lys Asn
                405                 410                 415

Asn Glu Met Asp Thr Lys Asn Leu Leu Asn Phe Glu Glu Asn Tyr Arg
            420                 425                 430

Asn Phe Asn Asn Ile Lys Lys Arg Asn Val Glu Lys Asn Asn Asn Val
        435                 440                 445

Leu His Glu Glu Cys Thr Ile Gly Asn Val Val Thr Ile Lys Glu Leu
    450                 455                 460

Glu Asp Ser Leu Gln Ile Phe Lys Asp Leu Asn Leu Glu Val Asp Ser
465                 470                 475                 480

Asn Gly Asn Leu Lys Lys Gly Ala Lys Thr Thr Asp Met Val Ile Ile
                485                 490                 495

Asn Asp Phe His Asn Ile Thr Asn Leu Gly Lys Lys Thr Val Asp Lys
            500                 505                 510

Leu Met Gln Val Gly Ile Asn Ile Val Val Gln Tyr Glu Pro His Asn
        515                 520                 525

Ile Glu Phe Ile Glu Lys Met Glu Pro Asn Asn Asp Asn Asn Asn Asn
    530                 535                 540

Asn Asn Asn Asn Asn Ile Leu Phe Tyr Val Asp Ile Lys Asn Ile Met
545                 550                 555                 560

Asn Ser Ser Glu Lys Asn Ile Lys Leu Ser Asn Ser Lys Gly Tyr Gly
                565                 570                 575

Leu Ile Leu Asn Gly Lys Glu Asp Ile Gln Thr Ile Lys Lys Ile Lys
            580                 585                 590

Glu Leu Asn Arg Arg Pro Leu Phe Ile Leu Leu Lys Ser Asp Asn Ile
        595                 600                 605

Tyr Glu His Val Leu Ile Thr Arg Arg Ile Asn Glu Leu Leu Gln Ser
    610                 615                 620

Leu Asn Ile Asn Ile Pro Tyr Ile His Tyr Val Asp Ile Asn Ser Asn
625                 630                 635                 640
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Asn Tyr Asp Asp Ile Leu Val Asn Ser Thr Leu Tyr Ala Gly Ser Cys
                645                 650                 655

Leu Met Asp Leu Met Gly Asp Gly Leu Ile Val Asn Val Thr Asn Asp
            660                 665                 670

Val Leu Thr Asn Lys Lys Lys Ile Glu Thr Lys Tyr Asp Glu Lys Glu
        675                 680                 685

Glu Val Glu Glu Glu Gly Asn Asn Lys Asp Ile His Arg Leu Leu Ser
    690                 695                 700

Arg Val Ala Leu Asn Ser Phe Leu Thr Leu Asn Ile Leu Gln Asp Thr
705                 710                 715                 720

Arg Ile Arg Leu Phe Lys Thr Asp Tyr Ile Ala Cys Pro Ser Cys Gly
                725                 730                 735

Arg Thr Leu Phe Asn Ile Gln Glu Thr Thr Lys Lys Ile Met Lys Leu
            740                 745                 750

Thr Gly His Leu Lys Gly Val Lys Ile Ala Val Met Gly Cys Ile Val
        755                 760                 765

Asn Gly Ile Gly Glu Met Ala Asp Ala His Phe Gly Tyr Val Gly Ser
    770                 775                 780

Ala Pro Lys Lys Ile Asp Leu Tyr Tyr Gly Lys Glu Leu Val Glu Arg
785                 790                 795                 800

Asn Ile Pro Glu Glu Glu Ala Cys Asp Lys Leu Ile Glu Leu Ile Lys
                805                 810                 815

Lys His Asn Lys Trp Lys Asp Pro
            820
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US 16299 (15696)

PTO/SB/103 (8-96)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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_____

_____

deren Beschreibung hier beigefügt ist, es sei denn (in diesem Falle Zutreffendes bitte ankreuzen), diese Erfindung

☐ wurde angemeldet am _____ unter der US-Anmeldenummer oder unter der Internationalen Anmeldenummer im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebiet des Patentwesens (PCT) _____ und am _____ abgeändert (falls zutreffend).

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As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

_____

_____

the specification of which is attached hereto unless the following box is checked:

☐ was filed on _____ as United States Application Number or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

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I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications
(Frühere ausländische Anmeldungen)

Priority Not Claimed
Priorität nicht beansprucht

(Number) (Nummer)	(Country) (Land)	(Day/Month/Year Filed) (Tag/Monat/Jahr der Anmeldung)	
	Germany		☐
	Germany		☐

Ich beanspruche hiermit Prioritätsvorteile unter Title 35, US-Code, § 119(e) aller US-Hilfsanmeldungen wie unten aufgezählt.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)

Ich beanspruche hiermit die mir unter Title 35, US-Code, § 120 zustehenden Vorteile aller unten aufgeführten US-Patentanmeldungen bzw. § 365(c) aller PCT internationalen Anmeldungen, welche die Vereinigten Staaten von Amerika benennen, und erkenne, insofern der Gegenstand eines jeden früheren Anspruchs dieser Patentanmeldung nicht in einer US-Patentanmeldung, bzw. PCT internationalen Anmeldung in in einer gemäß dem ersten Absatz von Title 35, US-Code, § 112 vorgeschriebenen Art und Weise offenbart wurde, meine Pflicht zur Offenbarung jeglicher Informationen an, die zur Prüfung der Patentfähigkeit in Einklang mit Title 37, Code of Federal Regulations, § 1.56 von Belang sind und die im Zeitraum zwischen dem Anmeldetag der früheren Patentanmeldung und dem nationalen oder im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebiet des Patentwesen (PCT) gültigen internationalen Anmeldetags bekannt geworden sind.

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)	(Status) (patented, pending, abandoned) (Status) (patentiert, schwebend, aufgegeben)
		Pending

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Postanschrift:

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POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: *(list name and registration number)*

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Hubbard, Brian J.,Reg. No.45,873; Kice, Warren B.
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901 Main Street, Suite 3100
Dallas, T
75202-3789

Direct Telephone Calls to: *(name and telephone number)* Warren B. Kice 214-651-5634

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Unterschrift des Erfinders Datum	Inventor's signature Date 28/02/01
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Staatsangehörigkeit	Citizenship Germany
Postanschrift	Post Office Address Breslauer Stresse 24 D-35398 GieBen, Germany
Vor- und Zuname des zweiten Miterfinders (falls zutreffend)	Full name of second joint inventor, if any
Unterschrift des zweiten Erfinders Datum	Second Inventor's signature Date
Wohnsitz	Residence
Staatsangehörigkeit	Citizenship
Postanschrift	Post Office Address

(Im Falle dritter und weiterer Miterfinder sind die entsprechenden Informationen und Unterschriften hinzuzufügen.)

(Supply similar information and signature for third and subsequent joint inventors.)